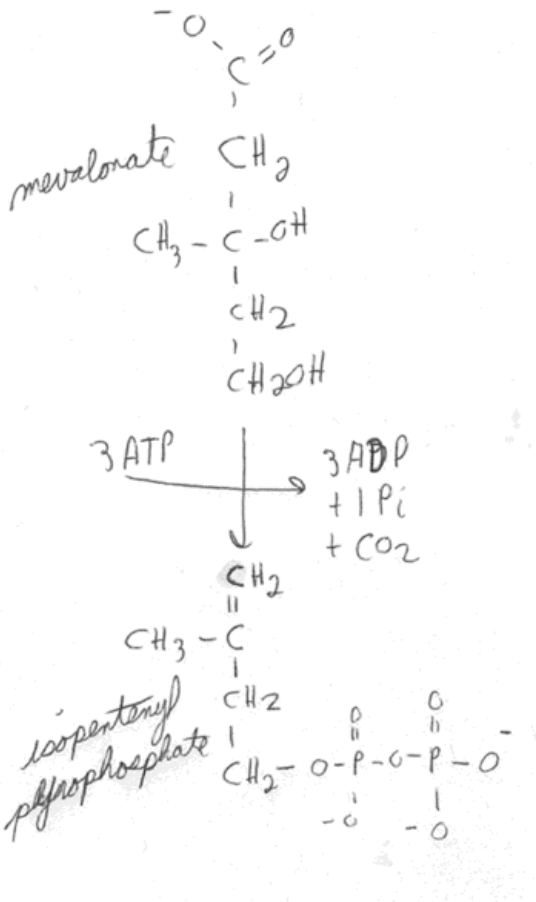
Cholesterol/Bile Acid Synthesis--8 Nov. 2002

1) Draw the reaction, including structures and stoichiometry, that converts mevalonate to isopentenyl pyrophosphate.



What compounds in addition to squalene are made from isopentenyl pyrophosphates (and/or geranyl and farnesyl pyrophosphates) and what are their functions. Ras and rho proteins contain farnesyl (C15) lipid modifications. Rab proteins contain geranylgeranyl (C20) lipid modifications. These lipid modifications anchor the rab, rho and ras proteins to membranes. Dolichol (N-linked oligosaccharide synthesis), ubiquinone (electron transport chain protein) and vitamin K and β-carotene either contain or are entirely made up of linked 5 carbon atom isopentenyl groups.

What type of chemical is squalene and what is the first compound in the cholesterol biosynthetic pathway to contain the steroid nucleus. Squalene is a terpene. Lanosterol is the first compound to contain the steroid nucleus.

2) What purpose do bile acids serve?

To emulsify fat (i.e. increase the surface area of the large fat droplets by breaking them into smaller droplets) making it a better substrate for pancreatic lipase.

What is the rate-limiting step in their biosynthesis and how is it regulated?

The rate limiting step is the addition of the 7□-hydroxyl group to cholesterol in a reaction catalyzed by 7□-hydroxylase (also called CYP7A). It is inhibited by increased levels of bile acids and activated by decreased levels of bile acids.

What purpose does conjugation of bile acids serve?

Conjugation results in bile acids that have lower pKs. This ensures that they are deprotonated at the pH of the ileum (about 6) and negatively charged. This makes them better detergents.

What is the enterohepatic circulation?

The enterohepatic circulation is a cycle: secretion of bile acids into the gall bladder which dumps bile into the duodenum, bile acids are then absorbed in the ileum and transported back to the liver by the hepatic portal venous system. This ensures that recycling of bile acids is very efficient as the liver almost completely absorbs them from the blood..

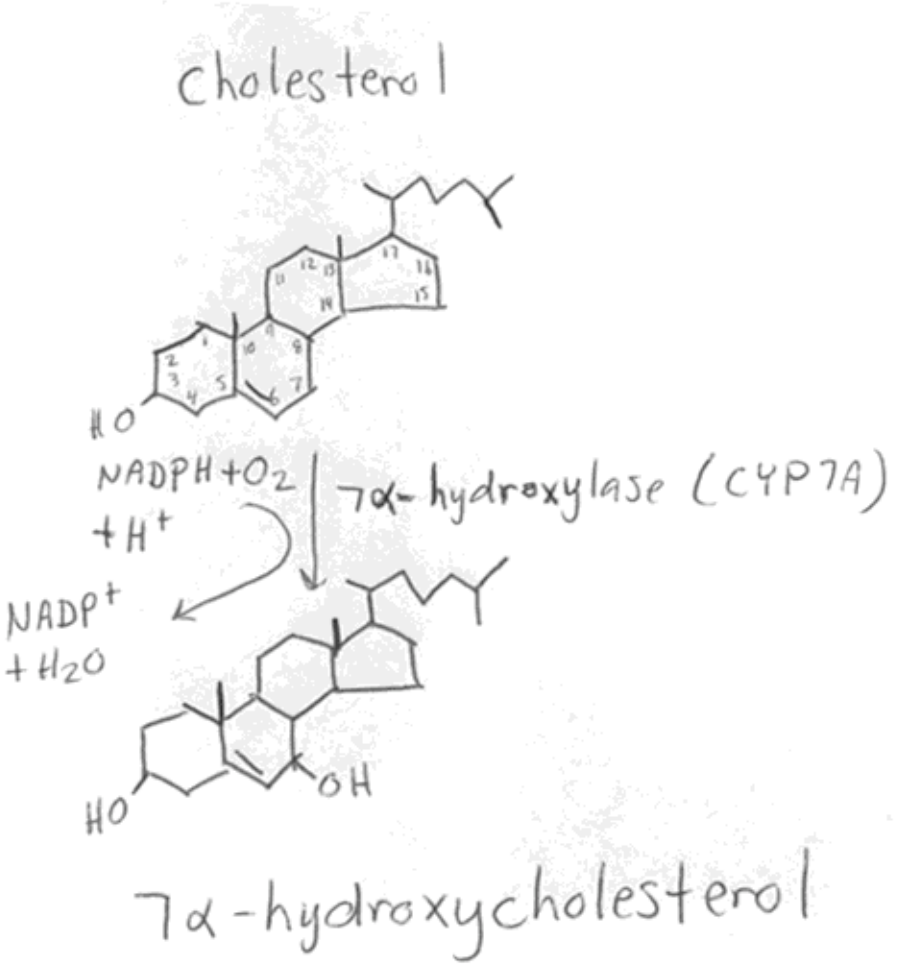
What purpose does loss of bile acids and cholesterol in the feces serve?

It is the only way to remove molecules that contain the steroid nucleus from the body.

What is the difference between a primary and a secondary bile acid?

Secondary bile acids do not have a 7-hydroxyl group. This has been removed by bacterial enzymes in the gut.

3) Write the reaction catalyzed by 7□-hydroxylase.



What class of enzyme is it?

7□-hydroxylase is a cytochrome P450 class of enzyme and within that class it is a **cytochrome P450 monooxygenase.** 7□-hydroxylase is quite specific for cholesterol.

Why is this class of enzymes important for biotransformation of drugs?

Cytochrome P450 class enzymes, of which there are dozens, are involved in oxidizing drugs as well as naturally occurring molecules in the body. Cytochrome P450 enzymes need the help of a cytochrome P450 reductase

enzyme in order to take electrons from NADPH and transfer them to the substrates. In the monooxygenase reaction of CYP7A, the substrates are molecular oxygen (O2) and cholesterol and the products are water and 7□-hydroxycholesterol. An additional electron and protons are acquired from other sources to complete the stoichiometry of the reaction. Note that this reaction cannot be done anaerobically because you need O2 as a substrate in this reaction. The oxidative reactions carried out by cytochrome P450 class enzymes are very important in modifying drugs to make them more hydrophilic which facilitates there excretion.